Remarks/Arguments

Claims 29, 30, 32 and 40-48 are pending in this application, claim 29 having been amended. Support for the amendment is at least at page 3, line 30; page 10, lines 18-23; page 12, lines 24-32; page 14, lines 3-14; Example 2, Table 2, and Figures 7-9. The amendment does not add new matter. The amendment has been made without prejudice, and without acquiescence to the outstanding rejections. Applicants specifically reserve the right to pursue any canceled subject matter in one or more continuing applications. Since the current amendments are believed to place this application in *prima facie* condition for allowance or, at least, present the claims in better form for consideration on appeal, their entry after final rejection is respectfully requested.

Claim Rejections - 35 USC 112, first paragraph - scope of enablement

Despite Applicants' earlier arguments, Claims 29, 30, 32, and 40-48 remain rejected as allegedly not being supported by an enabling disclosure in the specification. The Examiner acknowledged sufficient enablement solely for "a method of inhibiting fluprostenol-induced cardiac hypertrophy in rats."

In support of the rejection, the Examiner states that (1) the definition of "PGF2alpha-associated" cardiac hypertrophy is unclear; (2) the specification only demonstrates that rats administered fluprostenol develop cardiac hypertrophy; and (3) there is no teaching in the specification how to diagnose PGF2apha-associated cardiac hypertrophy.

Without acquiescing to the rejections, or the reasoning underlying the rejections, the claims, as currently amended, are drawn to the treatment of patients diagnosed with pressure overload-induced cardiac hypertrophy.

The test for enablement entails an analysis of whether one skilled in the art would have been able at the effective filing date to practice the invention using information disclosed in the application and information known in the art without undue or unreasonable experimentation (MPEP § 2164.01; see In *re Wands,* 858 F.2d 731, 8

USPQ 2d 1400, [Fed. Cir. 1988]). A finding of lack of enablement and determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re Wands* factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of ordinary skill in the art; 3) guidance provided in the specification; and 4) the state of the prior art. "[H]ow a teaching is set forth, by specific example or broad terminology, is not important"; and furthermore still, "limitations and examples in the specification do not generally limit what is covered by the claims" (MPEP § 2164.08). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* 448 F.2d 872, 878-79; 169 USPQ 759, 762 63 (2d Cir. 197 1), cert. denied, 404 U.S. 10 18, 30 L. Ed. 2d 666, 92 S. Ct. 680 (1972). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

Nature of the Invention and Level of Ordinary Skill in the Art

The invention concerns the use of a known polypeptide, IFN-γ, for the treatment of pressure overload induced cardiac hypertrophy. Although medical treatments generally have a relatively high degree of unpredictability, in the present case, this is moderated by the high level of skill in this field, which is represented by a medical degree or Ph.D. and several years of experience.

Guidance provided in the specification

The Examiner's assertion that "the specification only demonstrates that rats administered fluprostenol develop cardiac hypertrophy" is clearly misplaced. The specification provides a detailed disclosure of cardiac hypertrophy of various causes, including pressure overload-induced cardiac hypertrophy. In addition to the general disclosure provided, for example, at page 10, lines 18-23; page 12, lines 24-32; and page 14, lines 3-14, Example 2 presents experimental data obtained in a well known rodent model of pressure overload. In particular, Example 2 shows that in rats pressure overload generated by abdominal aortic constriction results in cardiac hypertrophy, as evidenced by substantial increases in absolute heart, atrial, ventricular, and left ventricular weights. In this model of pressure overload-induced hypertrophy, treatment with IFN-γ significantly attenuated cardiac hypertrophy (Table 2 and Figures 7 and 8). The results show an approximately 10-12% decrease in heart weight, ventricular weight and left ventricular weight normalized to body weight between the vehicle and treatment groups (Table 2 and Figures 7 and 8). The data in Table 2 additionally shows an approximately 20% reduction in the atrial weight to body weight ratio in IFN-γ-treated rats compared to vehicle controls. Mean, systolic and diastolic arterial pressure were markedly higher in rats with aortic constriction compared to sham-operated controls, and the incremental increase in arterial pressure was not different between banded rats treated with IFN-γ or vehicle (Figure 9). Thus, the attenuation of cardiac hypertrophy in banded rats receiving IFN-γ was not due to an alteration in afterload.

The state of the prior art

The terms "pressure overload induced hypertrophy" and "pressure overload hypertrophy" are expressions of the art, which were well known and extensively used by those skilled in the art well before the priority date of this application. It was also known that human patients can develop cardiac hypertrophy, in particular left ventricular hypertrophy as a result of pressure overload of various causes, including aortic stenosis,

systemic arterial hypertension, hypertension developed in dialysis patients, and the like. For example, Shahi *et al., The Lancet* 336:458-461 (1990) (Reference # 43 of record) discuss the correlation between systemic hypertension and left ventricular hypertrophy in human patients. Rossi *et al., Am. Heart J.* 124:700-709 (1992) (Reference #41 of record) discuss pressure overload cardiac hypertrophy, and the resultant structural remodeling of the myocardium, which is characterized as "probably a major contributory factor to the increased morbidity and mortality rates that are associated with pressure overload cardiac hypertrophy." The same paper describes the use of aortic-constricted rats, in an experiment very similar to that described in the present application, to test the effect of captopril on the prevention and regression of interstitial fibrosis in pressure overload cardiac hypertrophy. In the discussion, citing Swynghedauw and Delcayre, *Pathobiol Annu.* 12:137-83 (1982), the authors refer to constriction of the abdominal aorta, just below the diaphragm, as being "postulated as an experimental model of pressure overload cardiac hypertrophy: (page 704, second column). Pressure overload hypertrophy in hemodialysis patients is discussed by Lopez-Gomez, *Kidney Int. Suppl.* 68:S92-8 (1998) (copy enclosed). Severe pressure overload hypertrophy in patients with aortic stenosis is discussed by Matter *et al., Circulation* 99:2396-2401 (1999).

Applicants submit that, in view of the detailed guidance provided in the specification, including data in a well accepted animal model, the extensive knowledge in the art at the time the invention was made, and the relatively high level of skill of those skilled in the pertinent art, one of ordinary skill in the art knows how to practice the invention within the full scope of the claims, without undue experimentation. Accordingly, the Examiner is respectfully requested to withdraw the present rejection.

All claims are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39766-0068A2D1). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: May 13, 2005

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Effect of NO Donors on LV Diastolic Function in Patients With Severe Pressure-Overload Hypertrophy

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Background—Previous experimental studies have shown that nitric oxide (NO) modulates cardiac function by an abbreviation of systolic contraction and an enhancement of diastolic relaxation. However, the response to NO donors of patients with severe pressure-overload hypertrophy and diastolic dysfunction is unknown.

Methods and Results—Intracoronary NO donors were given to 17 patients with severe aortic stenosis. A dose-response curve was obtained with nitroglycerin (30, 90, and 150 μg) in 11 patients and sodium nitroprusside (1, 2, and 4 μg/min) in 6. Left ventricular (LV) high-fidelity pressure measurements with simultaneous LV angiograms were performed at baseline and after the maximal dose of NO. The dose-response curve for intracoronary NO donors showed a marked fall in LV end-diastolic pressure, from 23 to 14 mm Hg (−39%; $P<0.0001$), whereas LV peak systolic pressure fell only slightly, from 206 to 196 mm Hg (−4%; $P<0.01$). End-diastolic chamber stiffness decreased from 0.12 to 0.07 mm Hg/mL ($P<0.0001$) and end-systolic stiffness from 1.6 to 1.3 mm Hg/mL ($P<0.01$). Heart rate, right atrial pressure, LV ejection fraction, the time constant of isovolumic pressure decay (τ), and LV filling rates remained unchanged.

Conclusions—In patients with severe pressure-overload hypertrophy, intracoronary NO donors exert a marked decrease in LV end-diastolic pressure without affecting LV systolic pump function. Thus, the hypertrophied myocardium appears to be particularly susceptible to NO donors, with a marked improvement in diastolic function. **(*Circulation*. 1999;99:2396-2401.)**

Key Words: nitric oxide ■ nitroglycerin ■ sodium nitroprusside ■ hypertrophy ■ diastole

Nitric oxide (NO) is known to be an important determinant in the control of vascular tone.[1] However, its influence as a modulator of myocardial function (reviewed in Reference 2) has only recently been appreciated. Smith et al,[3] Brutsaert and Andries,[4] and Ramaciotti et al[5] pioneered the research investigating the role of the endocardial and vascular endothelium to modulate myocardial contraction and relaxation. These and subsequent studies have shown that NO- and/or cGMP-releasing substances increase diastolic cell length, decrease contractility, shorten ejection period, diminish contractile response to β-adrenergic agonists, and slow heart rate.[6–8] These findings have been confirmed in the human myocardium, demonstrating a reduction in left ventricular (LV) pressure and an improvement in LV diastolic distensibility after intracoronary administration of NO-releasing compounds in patients with normal LV function[9] and in transplant recipients.[10] However, the effect of NO donors on LV function in patients with severe pressure-overload hypertrophy and accompanying diastolic dysfunction is still unknown.

Thus, the purpose of the present study was to evaluate the effect of intracoronary NO donors on LV contraction and relaxation in patients with severe aortic stenosis.

Methods

Patient Characteristics

Fifteen men and 2 women (age, 58±10 years) were included in the present analysis. Eleven patients received intracoronary nitroglycerin (NTG) and 6, intracoronary sodium nitroprusside (SNP). All patients underwent diagnostic cardiac catheterization for symptomatic aortic stenosis (NYHA class, 2.2±0.3; mean gradient, 66±17 mm Hg; valve area, 0.7±17 cm^2; muscle mass index, 175±64 g/m^2). There were no significant differences between patients receiving either NTG or SNP with regard to baseline characteristics. Patients with significant coronary artery disease (>50% diameter stenosis), hypotension (systolic blood pressure <100 mm Hg), moderate to severe congestive heart failure (NYHA class III to IV) or age >75 years were excluded from the present analysis. The study protocol was approved by the local ethics committee, and informed consent was obtained from all patients.

Study Protocol

All vasoactive drugs were withheld for ≥24 hours before the procedure. Right and left heart catheterization was performed according to our protocol (Figure 1). Right-sided pressures were measured by a 6F Cournand catheter introduced from the right femoral vein and left-sided pressure by a 6F pigtail catheter introduced from the right femoral artery. Coronary angiography was carried out with nonionic contrast material (Iopamiro, Iopamidol 300; Sintetica AG). At the end of diagnostic angiography, an interval

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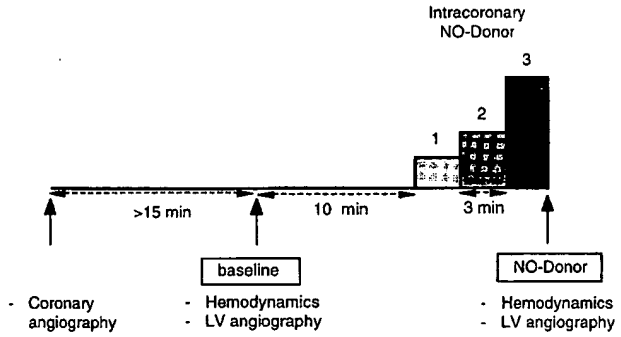

Figure 1. Study protocol. Angiographic measurements were performed at baseline and after maximal dose of NO donor. Pressures were recorded at baseline and after each dose of NO-releasing compound. Bar 1, NTG 30 μg or SNP 1 μg/min; bar 2, NTG 90 μg or SNP 2 μg/min; and bar 3, NTG 150 μg or SNP 4 μg/min.

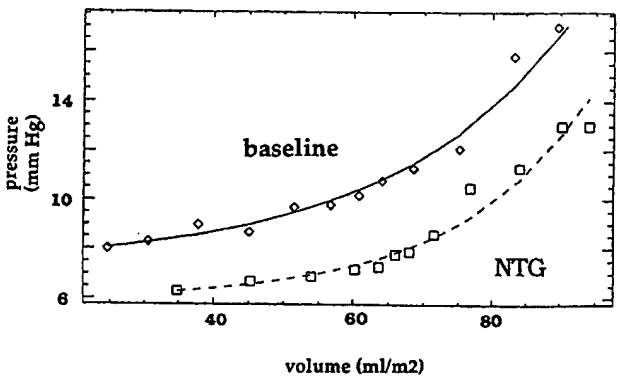

Figure 3. Diastolic pressure-volume curve in a patient with severe aortic stenosis before and after intracoronary NTG. Parallel downward shift of diastolic pressure-volume curve after NO donor.

of ≥15 minutes was allowed for dissipation of contrast effects. LV pressure was measured with a transseptally introduced 3F Millar catheter (Figure 2). A 6F coronary artery infusion catheter was placed in the left main coronary artery for intracoronary drug administration. Its position was confirmed at the beginning and at the end of the study by contrast injection. A dose-response curve was obtained for both NTG (Perlinganit, Schwarz Pharma AG) injections with increasing doses of 30, 90, and 150 μg and for SNP infusions with doses of 1, 2, and 4 μg/min (Nipride, Roche). Simultaneous biplane LV angiograms in the right and left anterior oblique projections were performed at baseline and after the maximal dose of the intracoronary NO donor with 40 to 50 mL of the nonionic contrast material (injection rate, 12 mL/s). Filming rate was 25 (n=7) or 50 (n=10) frames per second. The LV angiograms of 3 patients could not be quantitatively analyzed because of premature ventricular contractions (2 patients receiving NTG, 1 SNP). LV volumes were analyzed on a frame-by-frame basis by the area-length method.[11] LV muscle mass was calculated according to the method of Rackley et al.[12]

Data Analysis

LV systolic function was determined from LV systolic pressure, peak positive dP/dt, LV systolic volume, and LV ejection fraction. Systolic ejection time was calculated as the time interval from the beginning of the Q wave in the standard ECG to end systole, which was defined as the time of pressure crossover of the LV and aortic pressure curves.

LV diastolic function was estimated from LV diastolic pressure, peak negative dP/dt, LV diastolic volume, the time constant of isovolumic pressure decay (τ), and early and late peak filling rates. Rate of relaxation was calculated from the linear relationship between LV pressure and negative dP/dt by use of a shifting asymptote[13]: $P=P_0 \cdot e^{-t/T}+P_B$, where P=LV pressure (mm Hg), P_0=pressure at the time of peak negative dP/dt, t=time after peak negative dP/dt (ms), T=time constant of isovolumic pressure decay (ms), and P_B=pressure asymptote. LV diastolic filling was measured from instantaneous LV volumes. Early peak filling rate (mL/s) was determined during the first half of diastole and late peak filling rate during the second half. Passive-elastic properties were determined from the diastolic pressure-volume (Figure 3) and stress-strain relationships by use of an elastic model with shifting asymptote: $P=a^* \cdot e^{bV}+c^*$ and $S=a \cdot e^{\beta\epsilon}+c$, where P=LV pressure (mm Hg), a*=elastic constant (mm Hg), b=constant of chamber stiffness, V=LV volume (mL), c*=pressure asymptote (mm Hg), S=LV midwall circumferential wall stress (kdyne/cm^2), a=elastic constant (kdyne/cm^2), β=constant of myocardial stiffness, ϵ=La Grangian strain, and c=stress asymptote (kdyne/cm^2). End-diastolic and end-systolic chamber stiffness was calculated from the instantaneous pressure-volume relationship at end diastole and end systole: End-diastolic CS=LVEDP/EDV and end-systolic CS=LVESP/ESV, where CS=chamber stiffness, LVEDP=LV end-diastolic and LVESP=end-systolic pressure (mm Hg), and EDV=end-diastolic and ESV=end-systolic volume (mL). The chamber stiffness constant b was derived from the exponential curve fit to the diastolic portion of the LV pressure-volume relation.[14] The myocardial stiffness constant β was calculated from the curve fit to the diastolic portion of the stress-strain relation.[14]

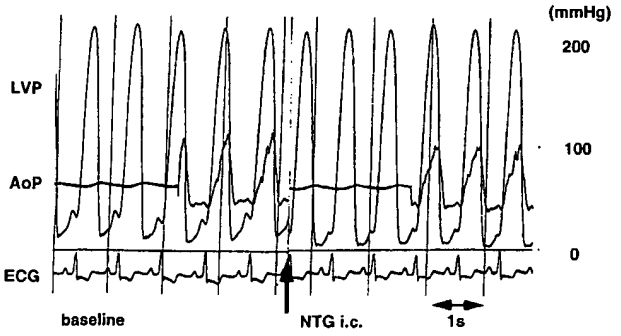

Figure 2. Representative LV pressure recording in a patient with aortic stenosis at baseline and after administration of NTG 150 μg IC. Note marked decrease in LV end-diastolic pressure after intracoronary NTG, whereas LV peak systolic pressure remains unchanged. LVP indicates LV pressure; AoP, aortic pressure.

Statistics

Hemodynamic and angiographic data at baseline and after intracoronary NO donors were compared by a paired Student's *t* test. Intragroup comparisons of the dose-response curve were carried out by a 2-way ANOVA for repeated measurements. Results are reported as mean±SD.

Results

LV Pressure Response to Intracoronary NO Donors

A representative pressure recording before and after intracoronary administration of NTG is shown in Figure 2. The dose-response curve (Figure 4) revealed a marked decrease of LV end-diastolic pressure with increasing doses of intracoronary NO donors (maximally −39% of baseline, $P<0.0001$). LV peak systolic pressure fell slightly but significantly (−4% of baseline, $P<0.01$).

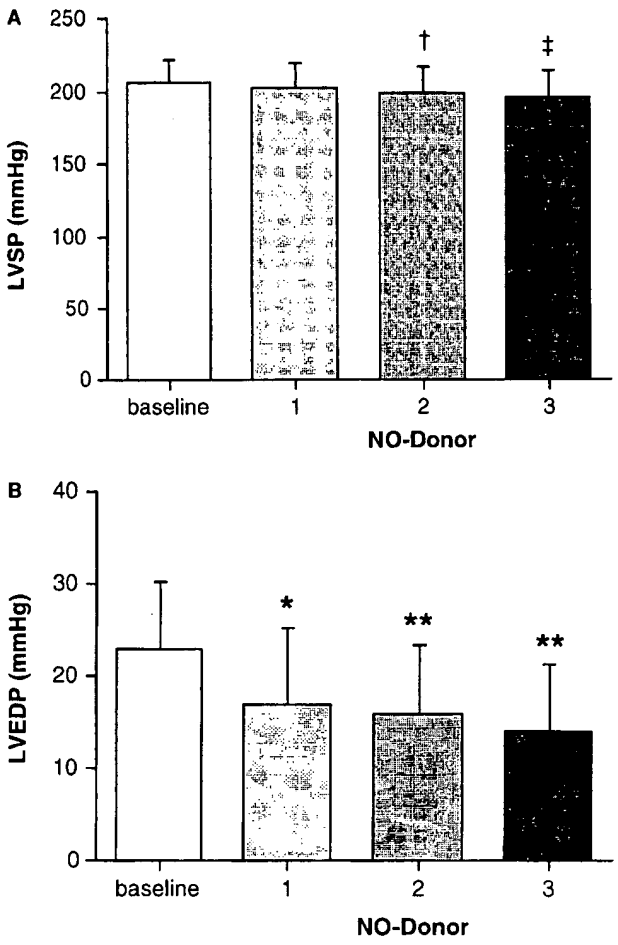

Figure 4. Dose-response curve of LV peak-systolic pressure (LVSP, A) and LV end-diastolic pressure (LVEDP, B) to intracoronary NO donors. LVSP is reduced at maximal dose by −4%, whereas LVEDP decreases by −39% of baseline value. Bar 1, NTG 30 μg or SNP 1 μg/min; bar 2, NTG 90 μg or SNP 2 μg/min; and bar 3, NTG 150 μg or SNP 4 μg/min. †$P<0.05$, ‡$P<0.01$, *$P<0.001$, **$P<0.0001$ vs baseline.

LV Systolic Parameters

In addition to the fall in LV end-diastolic and peak-systolic pressure, there was a decrease in LV end-systolic pressure ($P<0.0001$) and in peak ejection rate ($P<0.05$) after NO administration (Table 1).

Heart rate, right atrial pressure, LV ejection time, peak positive dP/dt, LV developed systolic pressure, LV end-diastolic volume, LV ejection fraction, and early and late peak filling rates remained unchanged after the NO donor.

LV Diastolic Function Parameters

Peak negative dP/dt decreased in parallel to the reduction in LV peak systolic pressure after intracoronary administration of the NO donor (Table 2). LV end-systolic chamber stiffness decreased slightly ($P<0.01$), whereas end-diastolic chamber stiffness decreased markedly ($P<0.0001$) after the NO donor. There was also a significant reduction in end-diastolic wall stress ($P<0.01$) and the stress asymptote c ($P<0.05$) after the NO donor. The time constant of LV pressure decay (τ), end-systolic wall stress, and LV chamber and myocardial stiffness remained unaffected, whereas the pressure asymptote c* of the diastolic pressure-volume relation decreased slightly. However, there was a downward shift of the LV diastolic pressure-volume curve in 7 of 17 patients (Figure 3). Furthermore, there was a significant correlation between LV end-diastolic pressure and pressure asymptote c* ($r=0.593$; $P<0.026$) or stress asymptote c ($r=0.637$; $P<0.015$).

The nitrovasodilators NTG and SNP are known to differ in their biotransformation of NO and the magnitude of their effects on preload and afterload after systemic administration.[15] The use of intracoronary NTG and intracoronary SNP allowed the exclusion of such differences (Table 3).

TABLE 1. Hemodynamic and Angiographic Data

	Baseline	NO Donor
Heart rate, bpm	65±9	65±9
Right atrial pressure, mm Hg	4.1±1.8	3.4±2.0
LV peak systolic pressure, mm Hg	206±21	196±22†
LV end-systolic pressure, mm Hg	106±12	93±11‡
LV end-diastolic pressure, mm Hg	23±8	14±8‡
LV developed systolic pressure, mm Hg	183±21	182±22
LV ejection time, ms	386±43	391±40
Peak positive dP/dt, mm Hg/s	1623±289	1665±287
LV ejection fraction, %	62±15	61±13
LV end-systolic volume index, mL/m^2	46±32	45±23
LV end-diastolic volume index, mL/m^2	113±31	110±23
Peak ejection rate, mL/s	53±34	33±44*
Early peak filling rate, mL/s	206±65	210±57
Late peak filling rate, mL/s	178±57	168±57

*$P<0.05$, †$P<0.01$, ‡$P<0.0001$ vs baseline.

Discussion

Diastolic dysfunction is a common finding in patients with severe aortic stenosis.[16] Its pathogenesis is manifold but can be explained by severe LV hypertrophy with a reduced Ca^{2+} reuptake into the sarcoplasmic reticulum, resulting in a defective excitation-contraction coupling; by elevated angiotensin II levels; or by a reduced capillary density and/or an increased collagen content.[17–21]

TABLE 2. LV Diastolic Function Parameters

	Baseline	NO Donor
Peak negative dP/dt, mm Hg/s	1554±205	1425±236*
τ, ms	66±9	64±7
LV end-systolic chamber stiffness, mm Hg/mL	1.60±0.74	1.30±0.50†
LV end-diastolic chamber stiffness, mm Hg/mL	0.12±0.04	0.07±0.03‡
Chamber stiffness constant b, mL^{-1}	0.053±0.023	0.058±0.028
Pressure asymptote c*, mm Hg	5.7±6.1	4.0±5.2
Myocardial stiffness constant β	15±7	17±12
Stress asymptote c, kdyne/cm^2	10.5±16.1	3.7±7.8*
LV end-systolic wall stress, kdyne/cm^2	138±101	122±56
LV end-diastolic wall stress, kdyne/cm^2	59±29	40±20†

*$P<0.05$, †$P<0.01$, ‡$P<0.0001$ vs baseline.

TABLE 3. Comparison of NTG vs SNP Effects

	NTG, Δ%	SNP, Δ%	*P*, NTG vs SNP
Systolic parameters			
LV peak systolic pressure	−6	−3	NS
LV end-systolic volume index	−10	+13	NS
LV end-systolic chamber stiffness	−18	−20	NS
Diastolic parameters			
LV end-diastolic pressure	−43	−32	NS
LV end-diastolic volume index	−6	+4	NS
LV end-diastolic chamber stiffness	−45	−34	NS
τ	−4	−1	NS
Right atrial pressure	−32	+12	NS

Δ% indicates % change from baseline.

Therapeutic approaches have been used to reduce LV diastolic filling pressure (dyspnea on exertion) and to improve subendocardial perfusion (angina pectoris) to ameliorate clinical symptoms and ultimately diastolic dysfunction. In severe aortic stenosis, valve replacement is the therapy of choice.[22] Nevertheless, aortic valve obstruction with moderate to severe LV hypertrophy may profit from therapy that is able to improve LV diastolic function.

The major findings of the present study were (1) that intracoronary NO donors improve diastolic function in patients with severe pressure-overload hypertrophy, with a decrease in LVEDP and a reduction in LV end-diastolic chamber stiffness and (2) that the hypertrophied myocardium seems to be particularly susceptible to NO donors, with a marked improvement in diastolic function.

Pathophysiological Mechanisms

Recent reports have underlined the role of NO as a modulator of cardiac function.[2] In isolated cardiomyocytes and papillary muscles, NO- and cGMP-releasing substances are associated with a decrease in systolic cell length and an improvement in diastolic relaxation.[3,23] This has been attributed to either a desensitization of myofilaments to Ca^{2+},[6] reaction of NO with oxygen radicals to form toxic peroxynitrites,[24] or binding of NO to the iron-containing proteins, such as those in the respiratory chain of the mitochondria.[25,26]

Similar data have been obtained in Langendorf preparations[7] and animal models[27] after administration of NO-releasing compounds, revealing a decrease in systolic contraction and an improvement in diastolic relaxation. Complementary results were reported by Paulus and coworkers after bicoronary administration of SNP in healthy patients[9] or infusion of substance P in transplant recipients,[10] with a decrease in LV filling pressure and an increase in LV distensibility.

Effect of NO Donors in LV Hypertrophy

In contrast to the previous findings of Paulus et al,[9] NO donors led to a pronounced decrease in LV end-diastolic pressure but had no effect on LV systolic pump function.

Similar observations have been reported with the use of intracoronary ACE inhibitors in patients with pressure-overload LV hypertrophy.[28] A decrease in LV filling pressure with an improvement in regional LV relaxation was found after intracoronary enalapril. These effects may be in part NO-mediated by the reduced degradation of bradykinin.[29] Other studies have shown a link between ACE inhibition and NO effects under in vitro[30] and in vivo conditions.[31] Thus, NO may contribute to the beneficial effects of ACE inhibitors with regard to LV diastolic function. However, the physiological relevance of NO in this setting remains speculative.

It must be pointed out that in our patients with pressure-overload hypertrophy, administration of intracoronary NO decreased LV filling pressures without affecting LV volumes. This combination suggests a parallel downward shift of the LV pressure-volume relation (Figure 3), which was seen in nearly half of our patients and which implies a change in LV distensibility. This trend was supported by a decrease in LV end-diastolic chamber stiffness, $\Delta P/\Delta V$. However, the chamber and myocardial stiffness constant b or β did not show a significant change after NO donors. This apparent contradiction can be explained by the fact that there was a parallel downward shift of the pressure-volume relation without a change in slope (resulting in an unchanged b or β), whereas the pressure asymptote c* decreased slightly and the stress asymptote c significantly (Table 3). Furthermore, there was a significant correlation between LV end-diastolic pressure and the pressure asymptote c* or stress asymptote c. Taken together, these findings support the concept of a downward shift of the diastolic pressure-volume curve in response to intracoronary NO donors, which was also observed by Paulus et al.[9]

LV end-diastolic pressure is known to be influenced by external forces, such as the pericardium and right ventricular filling pressure.[32,33] Thus, biventricular interaction may account for the parallel decrease of both right ventricular and LV filling pressures in the context of pure preload reduction.[34] However, to avoid systemic effects, NO donors were administered by the intracoronary route, and the fall in LV end-diastolic pressure was not achieved by a change in right atrial pressure, suggesting a direct effect of NO on the myocardium.

There were minor changes in LV systolic function after NO donors. A decrease in peak systolic pressure and peak ejection rate would ordinarily suggest a decline in contractility. However, developed pressure and LV ejection fraction remained stable, indicating no change in LV contractile state. Accordingly, a decline in peak ejection rate associated with a decrease in end-diastolic wall stress and stable end-diastolic volume may be caused by an effect via the Frank-Starling mechanism.

Role of NO in LV Hypertrophy

Why does the hypertrophied myocardium differ from the normal myocardium in its response to NO donors? Is constitutive NO synthase (NOS) activity impaired in the hypertrophied myocardium compared with the normal heart, or are some of the downstream signals of NO altered in LV hypertrophy?

Two recent reports from animal models of pressure-overload hypertrophy may provide some explanations. The

authors administered SNP to isolated rat cardiomyocytes[35] and demonstrated a decrease in systolic contraction and an increase in diastolic cell length in normal but not in hypertrophied myocytes. These findings were explained by a blunting of the downstream signaling effect of cGMP on the sodium proton exchange. In normal cardiomyocytes, this leads to an increase in contraction, whereas this response is impaired in hypertrophied cardiomyocytes.

In a canine model of pressure-overload hypertrophy, basal and stimulated myocardial cGMP levels after the NO donor morpholinosynonimine were higher in LV hypertrophy than in controls.[29] However, the NOS inhibitor N^{ω}-nitro-L-arginine methyl ester had no effect on cGMP levels in either group. It is of interest that LV mechanics remained unaffected after the NO donor in the group with hypertrophy, whereas it changed in the control group. These findings suggest that animals with hypertrophy have increased myocardial cGMP levels that are independent of NOS activity.

No data on myocardial NOS activity in pressure-overload hypertrophy in humans are available. The levels of constitutive NOS levels could not be determined because no myocardial biopsies were performed in the present study.

Taken together, the data derived from the animal experiments support our findings, which showed no effect of NO donors on contraction or relaxation in patients with severe pressure-overload hypertrophy. They suggest that the downstream targets of NO in the hypertrophic myocardium may be less responsive to NO than the normal one.

Clinical Implications

Our data show that NO donors improve diastolic function in patients with severe LV hypertrophy. LVEDP dropped by 39% after small intracoronary doses of NO donors, whereas systolic pump function remained unchanged. In contrast, Paulus and coworkers[9] reported a 21% decrease in baseline peak LVEDP after 4 μg/min SNP in patients without cardiac disease. Because the hypertrophied myocardium is associated with a high incidence of LV diastolic dysfunction,[16] NO donors may be particularly suitable for decreasing elevated diastolic filling pressures. Thus, nitrovasodilators may be able to reduce lung congestion and dyspnea on exertion on a short-term basis. Their long-term effect remains to be determined.

Study Limitations

1. SNP and NTG were used as NO donors for the purpose of the present study. These substances differ in their biotransformation of NO. NTG requires the presence of *S*-thiol enzymes, whereas SNP liberates NO spontaneously.[15] It is known that nitrovasodilators do not accurately mimic endothelial or myocardial NO release. However, these compounds are widely used in clinical application for acute and chronic treatment of coronary and valvular heart disease.

2. Single coronary administration of the NO donors was used instead of bicoronary infusions. This may have led to an underestimation of the NO donor effect, but systemic side effects may have been minimized.

3. A control group of patients with administration of vehicle was not included. A previous collaborative study from our laboratory showed no effect on diastolic function with the intracoronary infusion of vehicle (normal saline) and repeated angiography in patients with severe aortic stenosis.[28]

Conclusions

The present study shows that administration of small intracoronary doses of NO donors leads to a marked decrease in LV filling pressure, suggesting that the hypertrophied myocardium appears to be particularly susceptible for exogenously administered NO donors. This may be explained by either a reduced production or release of NO by the endothelium in the hypertrophied myocardium.

In contrast to previous studies in healthy volunteers, the hypertrophied ventricle shows no effect of intracoronary NO donors on LV contraction and relaxation. This effect may be explained by a blunting of the downstream signaling effects of cGMP in the hypertrophied cardiomyocytes due to an increased constitutive NOS activity[35] and/or increased guanylate cyclase activity.[29]

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Blood pressure, left ventricular hypertrophy and long-term prognosis in hemodialysis patients

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Blood pressure, left ventricular hypertrophy and long-term prognosis in hemodialysis patients. Cardiovascular events are the main cause of death in patients with chronic renal failure who are treated with hemodialysis. Hypertension is frequent among dialysis patients and may be a major cause of mortality, although epidemiological studies are controversial in this regard. This disparity in results may be the consequence of an inadequate definition of hypertension in dialysis patients as well as the interaction with hypertension with other risk factors such as malnutrition or left ventricular hypertrophy (LVH), which are strong predictors of death. Although the goal of blood pressure in dialysis has not been established yet, it seems that predialysis blood pressure levels lower than 150/90 mm Hg must be achieved for patients to avoid complications. LVH is very frequent among dialysis patients and starts early in the progression of chronic renal failure. Hypertension is the main cause for its development, but other potentially reversible factors such as anemia, volume overload, secondary hyperparathyroidism, dose of dialysis or malnutrition may also be implicated. Hence, an adequate management of patients on hemodialysis must include the strict control of blood pressure, preferably with angiotensin converting enzyme (ACE) inhibitors, together with those early measures in order to avoid the development of the other causes of LVH or to treat them when they already exist.

Patients on chronic hemodialysis have an age-adjusted death rate 3.5 times higher than the general population [1]. This poor prognosis can be explained by their high comorbidity [2, 3]. Cardiovascular events are the main cause of death, 54% among hemodialysis patients in USA [2] and 47% in Europe (Valderrábano et al, this issue). Arteriosclerosis is more frequent, severe and appears early in these patients [4]. Hypertension has been shown to be a strong predictor of mortality in general population [5]. It has generally been accepted that the blood pressure (BP) linked to a low cardiovascular risk is that lower than 120/80 mm Hg [6] and in this sense, about 80% of patients on hemodialysis have a BP higher than this level [7]. All these data suggest that hypertension would be a major cause of mortality in dialysis patients, however, the results of epidemiological studies are controversial.

Some published studies show a direct relationship between both systolic and diastolic predialysis BP and the mortality rate [8–11]. Antihypertensive therapy improves the one-year mortality rate irrespective of the level of BP control [12]. Sometimes it is necessary to look for the association of several cardiovascular factors, such as hypercholesterolemia, systolic BP, and cigarette smoking, to find a relationship with the mortality rate [13]. Moreover, hypertension has been implicated in the development of left ventricular hypertrophy (LVH) [3], arteriosclerosis [4] and ischemic cardiomyopathy [14]. In contrast, other authors show that high BP is not an independent risk factor of death [15–18], even among diabetic patients [19]. Greaves and Sharpe found an inverse relationship between predialysis diastolic BP at the beginning of hemodialysis therapy and the gross mortality rate [1]. These authors also describe that malnourished patients often have a low diastolic BP, suggesting that nutritional factors would be a strong predictor of mortality in dialysis patients [1, 20]. Moreover, an inverse relationship between BP and mortality rate has also been described to be a result of congestive heart failure [3]. Only 6.6% of long-term surviving patients on hemodialysis have a systolic BP lower than 110 mm Hg [21], and a systolic dysfunction must be suspected in these cases.

In our experience, neither systolic or diastolic BP are independent risk factors of death in hemodialysis patients. A study of survival cofactors in a cohort of 193 patients with more than six months on hemodialysis was performed. The clinical and demographic characteristics of the patient cohort at six months of patient entry on hemodialysis are shown in Table 1. Patients were evaluated at six months from the onset of hemodialysis and the results were related with the outcome data after a mean period of 81 ± 65 months. At the end of the study, 82 patients had died, 11 were lost to follow-up, and 100 were alive on treatment. Seventy-three percent of them were on hemodialysis with low permeability and compatible membranes, and the remaining patients used high performance membranes.

Key words: hypertension, left ventricular hypertrophy, cardiac complications of dialysis, hyperparathyroidism, adequacy of dialysis, anemia.

Table 1. Characteristics of the study population

Age *years*	60 ± 15 (19–85)
Male/female %	60/40
Cause of chronic renal failure %	
Diabetes mellitus	19
Primary glomerulonephritis	16
Secondary glomerulonephritis	6
Polycystic disease	8
Nephroangiosclerosis	6
Other etiology	16
Unknown disease	11
Predialysis blood pressure *mm Hg*	144/79 ± 21/12.5
Postdialysis blood pressure mm Hg	125/71 ± 23/13
Patients with antihypertensive therapy %	32
LVH in echocardiography (168 pat) %	88
Evaluated parameters were	
PCR *g/kg/day*	1.02 ± 0.29
Kt/V (Daugirdas II)	1.09 ± 0.25
Relationship between Kt/V and PCR (N = 192)	r = 0.424, P < 0.001; PCR = 0.475 + 0.506*Kt/V
Predialysis creatinine *mol/liter*	844 ± 255
Albumin *g/liter*	41 ± 6
Total CO_2 *mmol/liter*	22.3 ± 3.6
Serum iPTH *pg/ml*	319 ± 334
Hematocrit %	30.3 ± 5.1
Hemoglobin *g/dl*	10.1 (52% with rHuEPO)
Cholesterol *mmol/liter*	5.34 ± 1.42
Triglycerides *g/liter*	1.55 ± 1.18
HDL cholesterol *mmol/liter*	0.39 ± 0.13
LDL cholesterol *mmol/liter*	1.35 ± 0.43
Body mass index *kg/m²*	22.3 ± 4.4
Arm mean muscle circumference *cm*	22 ± 4

This is from a prospective cohort study of 193 patients who survived more than 6 months on hemodialysis (HD). Baseline evaluation 6 months after HD onset and posterior follow-up is 81 ± 65 months. Blood pressure pre- and post-HD average of 12 hemodialysis sessions at sixth months after the onset of HD. LVH is left ventricular hypertrophy. Values are expressed as mean ± SD.

Causes of death were: cardiovascular 27%, infectious disease 24%, dementia and cerebrovascular events 16%, unknown etiology in 12%, and malignancies 11%. In univariate analysis comparing the variables between death and survival patients, age, serum creatinine and albumin, protein catabolism rate (PCR), hemoglobin, arm mean muscle circumference (AMMC) and postdialysis systolic BP were significantly different between both groups at six months after starting dialysis. No differences were found in systolic and diastolic predialysis BP, postdialysis diastolic BP, left ventricular mass index (LVMI), Kt/V, total CO_2, PTH, serum cholesterol and triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol nor body mass index. Using Cox regression modeling, age alone, low serum creatinine and diabetes mellitus were independent risk factors of death.

The disparity in the results from the different studies may depend upon: (*a*) statistical analyses that do not clearly define the outcome risk factors for hemodialysis [22]; (*b*) interaction of hypertension with other risk factors such as malnutrition; (*c*) the controversy over an established adequate definition of hypertension in dialysis patients; and (*d*) the strong relationship between cardiovascular mortality and LVH, which is very influenced by factors other than hypertension. The last two aspects are reviewed in the next sections.

Table 2. Blood pressure (BP) pre- and post-hemodialysis (HD) and the next day (NDBP), in 40 hemodialysis patients

	Pre-HD BP	Post-HD BP	NDBP
		mm Hg	
Systolic BP	140 ± 21	120 ± 20	127 ± 20
Diastolic BP	79 ± 13	69 ± 11	73 ± 11

Data are the mean BP of the three HD sessions and at the next day in a week.

Correlations between: preHD systolic BP and systolic NDBP are r = 0.77, N = 40; PreHD diastolic BP and diastolic NDBP are r = 0.81, N = 40; Post-HD systolic BP and systolic NDBP are r = 0.89, N = 40; post-HD diastolic BP and diastolic NDBP, r = 0.86, N = 40; $P < 0.01$.

WHAT FACTORS INFLUENCE PATIENT BLOOD PRESSUE DURING HEMODIALYSIS?

When must the patient be considered hypertensive?

Hemodialysis sessions produce cyclic changes in sodium and water content that are related to BP. We studied the mean BP before and after three hemodialysis sessions from one week, and the results are compared with basal BP values obtained from the hospital during the three next days without hemodialysis (Table 2). Both predialysis and postdialysis BP had a strong relationship with basal BP, suggesting that BP obtained from a patient on hemodialysis could be an estimate of the basal BP, although the levels are different. Predialysis BP overestimated basal BP while postdialysis BP underestimated it, although the latter was closer to the basal BP value. The decrease of BP during hemodialysis was lesser in hypertensive patients. Postdialysis BP and the mean between pre- and post-hemodialysis BP values were more closely correlated with basal interdialysis BP. Some studies using 24- to 48-hour BP monitoring confirm these concepts [23]. LVH is better correlated with predialysis systolic BP [23] and nocturnal systolic BP. The loss of a BP circadian rhythm is frequently found in these patients, and more accentuated in hypertensive patients and those with volume overload [24, 25].

Blood pressure in hemodialysis patients depends mainly on the hydration state [26–28]. In our experience, BP does not change significantly throughout the first four years on hemodialysis (Table 3). There is no relationship between the interdialysis weight gain and the predialysis BP. Hypertensive patients do not seem to have a higher weight gain, although predialysis BP in each patient does have a good correlation with the weight gain. After the week's end, BP tends to be higher and is related with a higher weight gain. An increase of BP at the end of a hemodialysis session was found in 7% of all the sessions during a three month period in 40 patients. It could be related to a sympathetic reaction

Table 3. Blood pressure (BP) and interdialytic weight gain (IGW) in 40 patients during the first four years on hemodialysis

	Pre-HD BP *mm Hg*	Dry weight *kg*	Interdialytic weight gain *g*
4th T–first year	141 ± 21/79 ± 14	60 ± 10.1	1863 ± 965[a]
4th T–2nd year	143 ± 23/80 ± 13	60 ± 10.7	2159 ± 800
4th T–3rd year	144 ± 22/80 ± 12	60.5 ± 11.1	2185 ± 847
4th T–4th year	144 ± 24/79 ± 12	60.9 ± 11.4	2064 ± 796

Data are the mean of BP and interdialytic weight gain of all sessions during last trimester (T). No significant relationship was found between BP and IWG in the group, but in each patient.

[a] $P < 0.05$ vs. 2nd, 3rd and 4th year after beginning HD

Table 4. Changes in left ventricular dimensions and function after dialysis ($N = 12$)

	LV before dialysis	LV after dialysis	*P*
LVEDD *mm*	49.4 ± 8.3	42.1 ± 9.0	< 0.05
IVST *mm*	11.4 ± 2.4	11.6 ± 2.1	NS
LVPWT *mm*	11.9 ± 2.3	11.9 ± 1.1	NS
LVMI g/m^2	134.2 ± 41.0	105.9 ± 37.5	< 0.05
E WAVE *cm/sec*	95.6 ± 31.4	70.5 ± 22.4	< 0.05
A WAVE *cm/sec*	86.1 ± 20.0	78.9 ± 19.4	NS
% Shortening	33.7 ± 14.9	35.9 ± 14.6	NS
Ejection fraction	45.9 ± 16.4	48.7 ± 15.5	NS

Mean weight loss was 2.1 ± 0.6 kg. Abbreviations are: LVEDD, left ventricular end diastolic diameter; IVST, interventricular septum thickness; LVPWT, left ventricular posterior wall thickness; LVMI, left ventricular mass index.

in response either to an exaggerated ultrafiltration or to the antihypertensive agent's clearance by dialysis.

With all the previous arguments, it is difficult to establish which BP measurement has the higher prognostic value. No matter which method of measurement is used, however, several measurements of BP must be taken, and when it is higher than 150/90 mm Hg, the diagnosis of hypertension must be considered in that patient.

The prevalence of hypertension in hemodialysis patients is very different in the literature, ranging from 2 to 58% [9, 24]. In Tassim, France, with its longer duration of hemodialysis sessions and a Kt/V > 1.5 (mean 1.7), the prevalence of hypertensive patients is around 2% [8]. In our study, 28% of the patients had predialysis systolic BP higher than 150 mm Hg and 12% had diastolic BP higher than 90 mm Hg. Postdialysis measurements showed that 10% of the patients had systolic hypertension and only 1% had diastolic hypertension. Cheigh et al found that 58% of patients had systolic and 39% diastolic hypertension. These authors suggest that hypertension is not adequately controlled in hemodialysis patients because it is not an easy task [24]. Differences in the prevalence of hypertension found among the various studies are likely due to patient characteristics such as race, social and economic status, and etiology of CRF, but the characteristics of hemodialysis and an inadequate sodium balance are highly implicated.

LEFT VENTRICULAR HYPERTROPHY IN HEMODIALYSIS PATIENTS

Left ventricular hypertrophy (LVH) is a compensatory response of the left ventricle to increase hemodynamic load. This structural abnormality includes two patterns: concentric LVH, where the cause is a cardiac afterload due to hypertension, which induces a lateral expansion of cadiomyocytes as well as proliferation of fibroblasts. The second pattern is the excentric LVH, a response to cardiac overload from anemia, arteriovenous fistula or volume overload, which results in an elongation of the myocyte. LVH is also accompanied by a reduced capillarization with a decrease in O_2 diffusion [29, 30].

The prevalence of LVH among hemodialysis patients is very high [31]. It can appear very early in the progression of CRF and may be present at the start of dialysis treatment [32, 33]; LVH is an independent risk factor of death in patients on dialysis [32, 34]. Actually, about one-half of the deaths of dialysis patients are due to cardiovascular events [2], which strongly implicates LVH as a primary risk factor [17].

Some direct consequences of LVH include poor tolerance to ultrafiltration on hemodialysis, congestive hearth failure, arrhythmia, angina pectoris and myocardial infarction, all of which may contribute to a high cardiovascular mortality [17, 29, 35–37].

RISK FACTORS FOR LEFT VENTRICULAR HYPERTROPHY

Hypertension is the main cause for the development of LVH [3, 32, 38–40], but other potentially reversible factors such as anemia, volume overload, secondary hyperparathyroidism, uremia, dose of dialysis, and malnutrition may have an important role in its pathogenesis [41].

Anemia

Typically, anemia in CRF patients on dialysis is accompanied by an hyperdynamic state with an increase in cardiac output and LV volume overload, which are directly related with the development of LVH [42, 43]. This process may induce a loss of myocardial contractility and contribute to LV dysfunction. Moreover, anemia is an independent risk factor for cardiac morbidity and mortality in ESRD patients [39, 44].

Partial correction of anemia with recombinant human erythropoietin (rhEPO) is associated with a decrease in LVH, especially due to a reduction in LV end diastolic diameter that is independent of age [45, 46]. Radermacher and Koch reviewed fifteen published studies, including patients who were treated with rhEPO during a mean time of 45 weeks. A partial correction of anemia to a steady-state hematocrit of 32.9% was obtained, which resulted in approximately an 18% decline in the LV mass index [47]. However, the improvement of LV mass did not reach

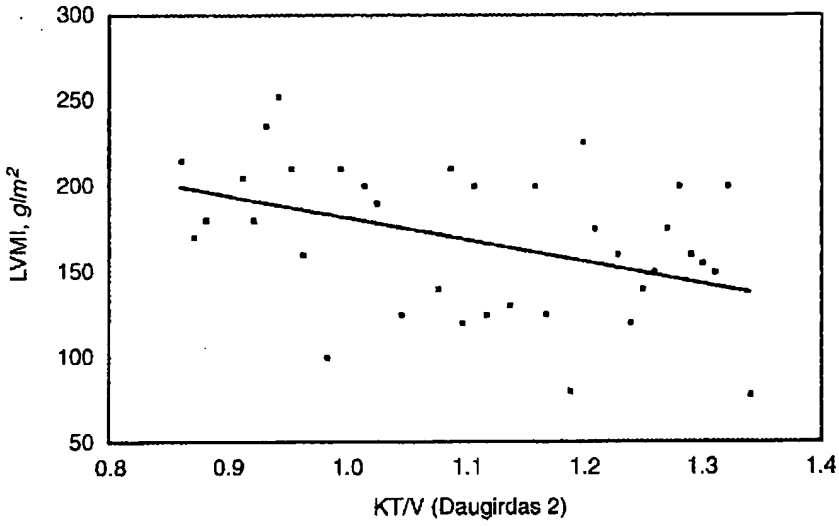

Fig. 1. Relationship between left ventricular mass index (LVMI) and Kt/V (Daugirdas 2) in 37 patients on hemodialysis ($r = -0.39$; $P = 0.01$)

normal values, suggesting either that this event was a multifactorial etiology where anemia was only a partial responsible factor, or that the hematocrit obtained was not sufficient for a complete normalization of LVH.

Beneficial effects of rhEPO therapy on LV mass may be counteracted by an increase in systemic vascular resistance, which may produce hypertension and cardiac overload [48, 49]. Withdrawing rhEPO therapy is followed by an increased in LV mass index and cardiac output with a decrease in peripheral vascular resistance [50], which confirms the role of rhEPO on the cardiac hemodynamics.

Volume overload

Salt and water retention is not only the major factor implicated in dialysis hypertension [28, 51, 52], but it may have a direct hemodynamic effect of increasing the cardiac preload. Echocardiographic findings show that interdialysis weight gain is accompanied by an increase in LVMI, mainly due to a rise in LV end diastolic diameter, which may have a long term effect on the development of LVH. Table 4 shows the changes in LV dimensions and function in 12 patients studied before and after a midweek hemodialysis session, with a mean weight loss of 2.1 kilograms.

Secondary hyperparathyroidism

Hyperparathyroidism (HPTH) is a common complication of CRF patients. It can be present very early in the decline of renal function, but mainly is found when an adequate control of calcium-phosphorous metabolism is not performed. In experimental models, it has been shown that parathyroid hormone (PTH) leads to cardiac fibrosis [53, 54] throughout the cardiac receptors for PTH in cardiac fibroblasts and myocardiocytes [55]. The relationship between HPTH and cardiac dysfunction is controversial [40, 56–58], but HPTH produces an increase in cytosolic free calcium that may result in chronotropic and inotropic effects on the myocardial cells [59, 60]. Together with other factors these changes may contribute to cardiac hyperthrophy [40, 57, 61]. In addition, a calcium phosphate deposition on the coronary microcirculation and atherosclerosis induced possibly by HPTH can predispose the patient to ischemic cardiomyopathy [62].

Until now, it has not been shown that a decline in serum levels of PTH after calcitriol treatment would be associated with an improvement of LVH. We did not find a significant relationship between PTH levels and LVMI in a group of 37 patients on hemodialysis. However, severe HPTH may play a certain role in the genesis of LVH. In this regard, we studied 12 patients on hemodialysis before and six months after total parathyroidectomy, using echocardiography. LVMI decreased significantly, which overall was due to a lower LV end diastolic diameter, but we also found an increase in hematocrit. Hence, these findings could not explain the true influence of the decrease in PTH levels *per se* on the cardiac hypertrophy, because the beneficial effect could partially be explained by the improvement of anemia [63].

Dialysis dose

There is some direct evidence that the dialysis dose is inversely related with both gross and cardiovascular mortality in hemodialysis patients [64–66]m and directly related with an improvement in cardiac structure abnormalities and dysfunction [67]. We studied 37 normotensive patients who had no previous ischemic heart disease, valvular disease or specific heart treatment. Patients were classified into two groups according to a Kt/V higher or lower than 1.1. We found a significant correlation between LV end diastolic diameter and Kt/V. A higher prevalence of LV dilation was also found in the group

with the lower dose (36% vs 5%, $P < 0.005$). Moreover, Kt/V correlated to LVMI (Fig. 1). There were no differences in systolic function in the two groups, while diastolic dysfunction was more frequently found in the group with Kt/V < 1.1 (81.2% vs 38.0%, $P < 0.01$). The logistical regression model showed a significant association between lower dialysis dose and diastolic dysfunction (OR = 6.36; $P = 0.02$) independently from LVH. Thus, the dialysis dose must be considered to be a uremic cardiomyopathy-related factor in hemodialysis patients [68].

Malnutrition

Hypoalbuminemia has been independently related to both relative risk of death and LV dilation in dialysis patients [16, 20, 32, 38, 64, 69]. It also predisposes the patient to the development of both *de novo* congestive heart failure and *de novo* ischemic heart disease [37, 70]. This association may partially explain the adverse effect that malnutrition has on the survival, although the closed mechanism is not yet clarified.

MANAGEMENT OF ARTERIAL HYPERTENSION AND LEFT VENTRICULAR HYPERTROPHY

The management of cardiovascular problems of end-stage renal disease (ESRD) patients must be attended to carefully to prevent all of the risk factors and manifestations. Hypertension must be controlled in patients on hemodialysis to avoid an impairment of tolerance to dialysis and the risk of malnutrition. BP control needs to be associated with the treatment as well as to other factors implicated in the development of LVH, such as hyperparathyroidism, hypoalbuminemia and anemia. These measurements must be started early in the treatment and progression of CRF, to avoid the reported high prevalence of cardiovascular manifestations at the onset of dialytic therapy [32].

When both an adequate dose of hemodialysis, with a Kt/V higher than 1.2, and a sodium and fluid restriction are obtained, the number of hypertensive patients on hemodialysis should be very low. Then, these patients should be monitored each 48 hours to evaluate the characteristics of their BP profile.

Strict BP control in conjunction with antihypertensive therapy, including ACE inhibitors, calcium channel blockers and beta blockers, may induce a regression of LVH [71]. However, the reduction of LVMI after the antihypertensive therapy may not only be due to a better control of BP, because some drugs (such as ACE inhibitors) can result a decrease in angiotensin II levels, which has been shown to have a proliferative effect on cardiac fibroblasts and myocardiocytes, independently of the antihypertensive and hemodynamic effects of this group of drugs [72, 73]. In this sense, Cannella et al recently showed the beneficial effect of lisinopril on decreasing the LVMI in ten normotensive patients on hemodialysis [74]. However, more studies are required to determine both the best target BP and the most appropriate antihypertensive agents in hemodialysis patients.

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